

In the Specification:

Please amend the specification as shown:

Please delete the paragraph on page 8, lines 7-14 and replace it with the following paragraph:

FIG. 4 schematically summarizes the results of experiments showing that recombinant BmiAP directly suppresses caspase-9 but not caspase-3 or caspase-7. FIG. 4A: Recombinant active caspase-9 was incubated with Ac-LEHD-AFC (SEQ ID NO: 26) substrate in the presence or absence of various concentration of recombinant purified BmiAP or SfiAP. FIG. 4B: Recombinant caspase-3 was incubated with Ac-DEVD-AFC (SEQ ID NO: 27) substrate in the presence or absence of GST-XIAP, GST-BmiAP or 0.5 uM GST-SfiAP. FIG. 4C: Recombinant caspase-7 was incubated with Ac-DEVD-AFC (SEQ ID NO: 27) substrate in the presence or absence of GST-XIAP, GST-BmiAP or GST-SfiAP. Full details in Example 1, below.

Please delete the paragraph on page 28, line 30 to page 29, line 5 and replace it with the following paragraph:

Cell extracts and Caspase assays: Cytosolic extracts were prepared by using human embryonic kidney (HEK) 293 cells (see, e.g., Deveraux (1997) Nature 388:300-303). For initiating caspase activation, 1 uM horse heart cytochrome-c (Sigma) and 1 mM dATP was added to extracts, as described by Deveraux (1998) Embo J. 17:2215-2223). Caspase activity was assayed by release of 7-amino-4-trifluoromethyl-coumarin (AFC) from Ac-DEVD-AFC (SEQ ID NO: 27) or Ac-LEHD-AFC (SEQ ID NO: 26) (Calbiochem), using a spectrofluorimeter as described by Stennicke (1997) supra; Quan (1995) J. Biol. Chem. 270:10377-10379.

Please delete the paragraph on page 31, lines 18-54 and replace it with the following paragraph:

BmiAP coding region nucleotide sequence:

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1 ATGGAGTTGA CGAAAGTTGC TAAAAATGGA GCTGCCGCCA CGTTGGTGAT GTTAAAAAAT
61 GCGCGGGATG CAAAAATGCG ACCTTTCATT GGTCCGCTCA TGTTATCCTC GTGTGAGTCT
121 TCAACGACAT GCACACTCCC GTCACCTTCG TCGTCAGCTG ATAAAACGGA TAATCACGAC
181 ACATTCAACT TCCTTCCTGA TATGCCCGAC ATGCGTCGTG AAGAGGAACG TCTGAAAACA
241 TTTGATCAGT GGCCCGTTAC GTTTTGTACG CCGGAACAAT TGGCCCGCAA CGGATTCTAC
301 TACGTGGGTC GCGGCGACGA AGTGTGCTGT GCTTTCTGTA AGGTAGAAAT ATGAGGTGG
361 GTCGAAGGCG ACGATCCTGC CGCCGATCAT CGGAGATGGG CGGCCAGTG TCCCTTTGTA
421 CGAAAACAAA TGTATGCCAA CGCTGGGGGA GAGGCGACCG CTGTCGGTAG AGACGAATGT
481 GGGGCCAGTG CGGCCACGCA GCCTCCCCGC ATGCCCGGCC CCGTGCACGC GCGGTACTGC
541 ACCGAGGCCG CGCGGCTCGC CACCTTCAAG GACTGGCCGA GACGTATGCG CCAAAAACCC
601 GAGGAACTGG CAGAGGCCGG ATTCTTCTAT ACAGGCCAAG GTGACAAAAC GAAATGCTTC
661 TATTGCGACG GAGGGCTAAA AGATTGGGAA AGCGATGACG TTCCGTGGGA ACAGCACGCC
721 AGATGGTTCG ACCGCTGCGC GTACGTGCAA TTGGTGAAAG GACGTGACTA CATTGAGAAG
781 GTGAAGTCGG AGGCCACTGC GATATCTGCT AGCGAAGAAG AACAGGCCGC CACCAATGAT
841 TCGACTAAGA ACGTCGCCCA AGAGGGCGAG AAACATTTGG ATGACTCTAA AATATGTAAA
901 ATATGTTATT CCGAGGAGCG TAACGTGTGC TTCGTGCCGT GCGGCCACGT GGTGGCGTGG
961 GCCAAGTGCG CGCTGTGCGC GGACAAGTGC CCGATGTGTC GCAGGACGTT CACGAATGCG
1021 GTGCGGCTCT ACTTCTCGTG A (Residues 2733-3773 of SEQ ID NO: 1)

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Please delete the paragraph on page 34, lines 3-13 and replace it with the following paragraph:

Experiments demonstrated that BmiAP inhibited Bax-induced but not Fas-induced apoptosis in mammalian cells (i.e., BmiAP protects mammalian cells against Bax-induced but not Fas-induced apoptosis). Expression plasmid encoding Bax (FIG. 3A) or Fas (FIG. 3B) were co-transfected into HEK 293 cells with the indicated myc-tagged IAP expression plasmids. Percentage apoptosis was measured 24 to 36 hours post-transfection by 4'-6-diamidino-2-phenylindole (DAPI) staining (mean \pm S.D., n=3). Recombinant BmiAP (2 μ M) was added to cytosolic extracts (10 mg/ml) from HEK293 cells concurrently with the addition of 1 μ M cytochrome-c/10 mM dATP. After incubation at 30.degree. C. for 10 minutes, aliquots were withdrawn and assayed for caspase activity, as measured by release of AFC from Ac-DEVD-AFC (**SEQ ID NO: 27**) substrate (100 μ M). Data are presented in FIG. 3C as a percentage relative to control reaction in which cytochrome-c/dATP were added alone.

Please delete the paragraph on page 34, line 29 to page 35, line 8 and replace it with the following paragraph:

These results were further confirmed in a cell-free system in which exogenously added cytochrome-c, an agonist of the caspase-9 activating protein Apaf-1 (see, e.g., Zou (1997) Cell 90:405-413), induced activation of caspase-3 and similar effector proteases. BmiAP directly suppressed caspase-9, but not caspase-3 or caspase-7. This was measured by hydrolysis of Ac-DEVD-AFC (**SEQ ID NO: 27**), as described by Quan (1995) J. Biol. Chem. 270:10377-10379). Recombinant active (FIG. 4A) caspase-9 was added at 0.2 μ M and incubated at 37.degree. C. with Ac-LEHD-AFC (**SEQ ID NO: 26**) substrate (100 μ M) in the presence or absence of various concentration (0.2-1.6 μ M) of recombinant purified BmiAP or SfiAP. AFC release was measured continuously. In FIG. 4, data are expressed as a percentage relative to control reactions lacking IAPs, using rates determined from the linear portion of enzyme progress curves. Various control GST-fusion proteins had no inhibition effect.

Please delete the paragraph on page 35, lines 9-12 and replace it with the following paragraph:

Recombinant caspase-3 (2.6 nM) was incubated at 37.degree. C. with Ac-DEVD-AFC (**SEQ ID NO: 27**) substrate (100 μ M) in the presence or absence of 0.05 μ M GST-XIAP, 0.5 μ M GST-BmiAP (200 fold molar excess to caspase) or 0.5 μ M GST-SfiAP (200 molar excess) (FIG. 4B). AFC release was measured as above.

Please delete the paragraph on page 35, lines 13-23 and replace it with the following paragraph:

Recombinant caspase-7 (7.0 nM) was incubated at 37.degree. C. with Ac-DEVD-AFC (**SEQ ID NO: 27**) substrate (100 μ M) in the presence or absence of 0.14 μ M GST-XIAP, 0.7 μ M GST-BmiAP (100 fold molar excess relative to caspase or 0.7 μ M GST-SfiAP (100 molar excess) (FIG. 4C). AFC release was measured as above. In cytosolic extracts treated with cytochrome-c, recombinant BmiAP and positive control recombinant SfiAP completely blocked the hydrolysis of Ac-DEVD-AFC (**SEQ ID NO: 27**) whereas negative control recombinant XIAP-BIR1 had no effect on caspase activity (FIG. 4C). Since caspases-3 and -7 are common to both Bax and Fas pathways, these results demonstrate

that BmiAP, like SfiAP, inhibits the mitochondria/cytochrome-c pathway in mammalian cells, thus, suppressing apoptosis at a step upstream of caspases-3 and -7. This finding is supported by the observation that BmiAP does not inhibit caspases-3 and -7 in vitro.

Please delete the paragraph on page 35, line 24 to page 36, line 2 and replace it with the following paragraph:

These experiments demonstrated that BmiAP is a direct inhibitor of caspase-9. Purified recombinant BmiAP was incubated with purified recombinant caspase-9. Residual activity was measured using Ac-LEHD-AFC (**SEQ ID NO: 26**) as a substrate of caspase-9. BmiAP inhibited recombinant caspase-9 in a concentration-dependent manner. The relative amount of BmiAP required for caspase-9 inhibition was about 8 fold molar excess (FIG. 4A), similar to the results reported previous for SfiAP and XIAP (Deveraux (1999) supra; Huang (2000) supra; SfiAP was shown to directly inhibit caspase-9). Unlike XIAP, but similar to SfiAP, BmiAP did not inhibit recombinant caspase-3 and caspase-7 (caspases-3, -7 and -9 are involved in apoptotic pathway induced by Bax), suggesting a narrower range of caspases specificity compared to human XIAP (FIG. 4B and C).

Sequence Listing Section of the Application

Pursuant to 37 C.F.R. 1.121 (b)(2), please delete the current sequence listing section and replace it with the clean version of the sequence listing provided herewith. A marked up version of the sequence listing is additionally provided herewith showing changes to this section.